



# BENEFIT vs. RISK:

## HOW CDER APPROVES NEW DRUGS

Under current law, all new drugs need proof that they are effective and safe before they can be approved for marketing. No drug is absolutely safe ... there is always some risk of an adverse reaction. However, when a proposed drug's benefits outweigh known risks, the FDA's Center for Drug Evaluation and Research (CDER) considers it safe enough to approve.

The U.S. drug law first embraced the idea of risk vs. benefit nearly 37 years ago. Providing evidence of safety before marketing was first required by the Federal Food, Drug and Cosmetic Act in 1938. However, it was not until the Kefauver-Harris Drug Amendments of 1962 did firms have to show a drug's effectiveness before marketing.

Before any drug gets on the market today, CDER decides—as quickly as a thorough evaluation allows—whether the studies submitted by the drug's sponsor (usually the manufacturer) show it to be safe and effective for its intended use (see chart, “the NDA Review Process,” p. 22 ).

“Take AZT, for example,” says Robert Temple, M.D., director of the Office of Drug Evaluation I in CDER. (AZT stands for azidothymidine, the former generic name of the drug now known generally as zidovudine and marketed as Retrovir

to treat AIDS.) “It has significant toxicity. If you weren't quite sure it had a benefit, it would be hard to describe it as ‘safe.’ But we know from well-controlled studies, that it has a benefit. In the first large clinical study with the drug, there were 19 deaths in patients taking a placebo (an inactive substance), but only one death among those on AZT.”

Zidovudine was approved in 107 days, without cutting any corners. CDER expended an estimated eight staff years at a cost of \$600,000 on the drug's evaluation. That the review was so rapid was due largely to the fact that CDER was involved with the drug every step along the way from the start of clinical studies in AIDS patients. In addition, over the past few years, CDER has approved new protease inhibitors for treating HIV infection. All of these products were approved in a matter of months; one was approved in only

42 days. A 12 percent decline in U.S. AIDS-related deaths is partly attributed to the rapid review and approval of these components, as well as, early patient access to them.

CDER has taken steps in a number of ways to make urgently needed drugs available sooner. These are drugs used in treating serious or life-threatening diseases that have no good treatment. Under the accelerated approval rule, the Center can rely as a basis for drug approval on a reasonable surrogate endpoint, that is, a positive effect of a drug on a marker of the disease, rather than an actual, positive effect on survival of an illness. (An example of a marker would be CD4 cell counts, used to measure the strength of the immune system.) Usually, such a surrogate can be assessed much sooner. In accelerated approval, CDER approves the drug on the condition that the sponsor study the actual clinical benefit of the drug.

### Promising Experimental Drugs

Today's policies allow broader use of some investigational drugs before approval for marketing. These policies include the treatment IND (investigational new drug application) and the parallel track mechanism. (see, "A Drug Review Glossary," p. 38, and "FDA Finds New Ways to Speed Treatments to Patients," p. 29.)

Both allow promising drugs, not yet approved for marketing, to be used in expanded access protocols—relatively restricted studies in which the intent is to learn about the drug, especially its safety, and provide treatment for people with no real alternatives. These expanded access protocols require researchers to formally investigate the drug in well-controlled studies and to supply some evidence that the drug is likely to be helpful. "This expanded access does not represent just giving the drug out," Temple says. "The sponsor has

the obligation to develop the drug properly, so we will know whether it really is useful."

CDER actively participates in the drug development process, seeking to provide clear standards and expectations. Sponsors are encouraged to meet with CDER before conducting large-scale controlled clinical trials. At this conference, CDER gives advice about the design of the sponsor's study plan to ensure that the trials will be acceptable.

As Temple puts it, "We try to find and eliminate flaws in the individual studies and overall development plan that we know will give us trouble later on in the NDA (new drug application) review. We don't want people to carry out a large study that has no chance of being considered adequate and well controlled."

CDER provides guidelines on how to study particular classes of drugs and on how to submit and analyze data in the marketing application.

To ensure that institutional review boards meet FDA's rules for the protection of the rights and welfare of research subjects, the agency routinely inspects the boards every five years. If problems are found, the agency may inspect the facilities more often. Animal laboratories are routinely inspected every two years, or more often if a review division has a question about a specific study.

### Reviewing NDAs

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests; how the drug is constituted—its components and composition; results of the animal studies; how the drug behaves in the body; and how it is manufactured, processed and packaged. CDER requires samples of the drug and its labels.

Full reports of a drug's studies must be submitted so that CDER

can evaluate the data. The controlled clinical trials are especially important because they provide the only basis, under law, for demonstrating effectiveness. They answer the question: "Does this drug work for the proposed use?" The whole data bank is used to look for adverse effects. From analyses of the data, CDER reviewers assess the benefit-to-risk relationship (see "The Review Team," p. 38).

Human studies generate information that will be in the drug's professional labeling—the guidance approved by CDER on how to use the drug. This is the package insert that accompanies a drug in all shipments to physicians and pharmacies.

Whenever an NDA is submitted to CDER, the center lists it in a computer database that is monitored by FDA's division of scientific investigations. The division assigns field reviewers to make on-site inspections to verify that the work cited in the NDA is valid. Since more and more foreign studies are being accepted as primary evidence for drug approval, FDA has been doing a larger number of foreign inspections.

If CDER's evaluation of studies reveals major deficiencies, substantially more work by the sponsor may be needed, ranging from further analyses to the conduct of new studies—either case extends the evaluation time and delays approval.

"It's particularly important," Temple says, "that sponsors use the opportunities CDER offers during the IND to discuss the critical studies and overall plans, so that they know what we expect with respect to study design, conduct, and analysis. This can greatly reduce the chance that the application will recycle."

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bled. The most significant initiative used to speed the review of, and access to, new medicines was the agreement among FDA, Congress, and the pharmaceutical industry to the Prescription Drug User Fee Act (PDUFA) of 1992. The act allowed the agency to hire several hundred additional reviewers and support staff and expedite its move toward accepting computerized NDAs.

Industry and consumer response to gains made by CDER under PDUFA led, in part, to Congress's passage of the FDA Modernization Act, in November 1997. The act contains some of the most sweeping changes to the Food, Drug, and Cosmetic Act in 35 years. Of significant importance to CDER is the reauthorization of PDUFA, which extends the legislation through fiscal year 2002. It also holds CDER to tighter review standards.

"The center's success in meeting and exceeding the review performance goals agreed to in 1992 give confidence that it can rise to new challenges," says Murray Lumpkin, M.D., Deputy Center Director. "Currently, CDER is reviewing more than 90 percent of priority drug applications in six months or less; and standard drug applications in 12 months or less."

### Priorities

CDER classifies investigational new drug applications and new drug applications (NDAs) to assign review priority on the basis of the drug's chemical type and potential benefit. All drugs that offer a significant medical advance over existing therapies for any disease are considered priority drugs.

Which CDER review staff gets an NDA depends on the drug. For example, cancer treatments go the division of oncology drug products; contraceptive drugs go to the division of reproductive and urologic drug products. Generic drugs, quite naturally, go to the office of generic drugs. CDER frequently seeks advice from its standing advisory committees on drugs (see "Getting Outside Advice for Close Calls," p. 41). This is especially true when an approved decision is a close call.

To be sure approval decisions reflect the most recent safety data, CDER requires safety updates four months after the NDA is submitted, again after it sends the firm an "approvable letter," and at other times if necessary. Updates must report new adverse reactions and important changes in the frequency or severity of known effects.

After CDER's primary reviewers finish their evaluation, supervisory personnel often do an additional

review. Office directors generally take final action on new molecular entities, switches from prescription to OTC status, and other important actions, such as a major new use of a drug. Other approval decisions are made at the division level.

### Final Actions

In the final analysis, CDER's decision whether to approve a new drug for marketing boils down to two questions:

- Do the results of well-controlled studies provide substantial evidence of effectiveness?
- Do the results show the product is safe under the condition of use in the proposed labeling? Safe, in this context, means that the benefits of the drug appear to outweigh its risks.

When the review is complete, CDER writes the applicant to say the drug is approved for marketing; is approvable, provided minor changes are made; or is not approvable because of major problems. In the last case, the applicant can amend or withdraw the NDA or ask for a hearing. Once CDER approves the NDA, a drug is on the market as soon as the firm gets its production and distribution systems going. So, while change is inevitable and often desirable, there are some constants at the Food and Drug Administration: Safety and effectiveness and benefit vs. risk remain the pivotal issues in drug review.

## A Special System for OTC Drugs

The Center for Drug Evaluation and Research has always applied the same standards to nonprescription drugs as it does to prescription ones whenever proposed over-the-counter (OTC) products meet the criteria for new drugs.

An OTC drug product does not need specific approval before marketing so long as it meets its category's standards. Sometimes an approved prescription drug is deemed safe enough for self-use and is switched to OTC status.

In 1966, FDA contracted for a review of the effectiveness of all new drugs approved solely on the basis of their safety since passage of the 1938 Federal Food, Drug and Cosmetic Act. Special attention soon focused on OTC drugs: of the 512 OTC drug products evaluated, 75 percent lacked substantial evidence of effectiveness.

That was when FDA decided it was time to tackle a broader review of OTC drugs—no small job, considering that more than 300,000 products were on the market. Those products, however, involved only about 700 active ingredients. It didn't take long for CDER planners to decide on a strategy: classify the drugs by treatment category (antacids, laxatives, and so on) and evaluate the ingredients. So, rather than review thousands of, say, individual antacid products, CDER evaluated the far fewer active ingredients found in them.

That review, under CDER's Office of OTC Drug Evaluation, is a three-phase rulemaking process, which includes advisory panel recommendations, a tentative final monograph and a final monograph for each therapeutic class of drugs under consideration. The first phase was accomplished by advisory panels that considered drugs by class, to determine whether ingredients could be generally recognized as safe and effective for self-use. Their conclusions and recommendations were presented to FDA. The agency published these recommendations in the

*Federal Register* and requested public comment. Panel reports have been published on all drug classes.

A number of ingredients were taken off the market as a result of the advisory panels' OTC drug review. Among them were:

- camphorated oil, a liniment often accidentally ingested with frequently toxic results;
- hexachlorophene, once common in deodorant soaps, but now available only by prescription for special antimicrobial purposes because it may damage the central nervous system;

FDA's final monograph, the third phase, identifies those active ingredients that are generally recognized as safe and effective for specified uses and that may be marketed in OTC drug products. The monograph identifies labeling claims that may appear on the products. OTC drug products containing any active ingredient or labeling claim that is not so recognized must be removed from the market. Some products can be reformulated or appropriately relabeled. For ingredients or claims not included in the monograph, a manufacturer has the option of applying for

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- tribromsalan, removed from drugs and cosmetics because it was found to make skin extra sensitive to light;
- zirconium, still safe in most forms of antiperspirants, but removed from aerosols because of concern it could cause lung nodules.

For lack of proof of effectiveness, FDA banned some 200 ingredients in 1990, including products used to treat problems ranging from acne and dandruff to diarrhea and pain. In 1993, the agency banned several hundred more, including products for such problems as pain, digestive upsets, menstrual symptoms, and skin rashes.

During the second phase, FDA presented its tentative conclusions. The proposed rule allows time for public comment and for submission of new data.

marketing approval through the new drug approval procedures. A manufacturer may petition to amend the final monograph to include additional ingredients or to modify labeling. However, the firm may neither market the drug, nor use the labeling claim until the NDA is approved or the final monograph is amended.

FDA expects to complete the OTC review by publishing final rules within the next few years. The "Milestone List of OTC Rulemakings" and the "OTC Drug Review Ingredients Status Report" are available on the Internet at: [www.fda.gov/cder/otc/index.htm](http://www.fda.gov/cder/otc/index.htm).

## The Evolution of U.S. Drug Law

FDA acts as a public health protector by ensuring that all drugs on the market are safe and effective. Authority to do this comes from the 1938 Federal Food, Drug and Cosmetic Act, a law that has undergone many changes over the years, just as it changed earlier drug regulation. Some of the major milestones in the evolution of the U.S. drug law are:

- **Food and Drugs Act (1906):** This first drug law required only that drugs meet standards of strength and purity. The burden of proof was on FDA to show that a drug's labeling was false and fraudulent before it could be taken off the market.
- **Federal Food, Drug and Cosmetic Act (1938):** A bill was introduced in the Senate in 1933 to completely revise the 1906 drug law—widely recognized then as being obsolete. But congressional action was stalled. It took a tragedy in which 107 people died from a poisonous ingredient in "Elixir Sulfanilamide" to promote passage of revised legislation that, for the first time, required a manufacturer to prove the safety of a drug before it could be marketed.
- **Durham-Humphrey Amendment (1951):** Until this law, there was no requirement that any drug be labeled for sale by prescription only. The amendment defined prescription drugs as those unsafe for self-medication and which should be used only under a doctor's supervision.
- **Kefauver-Harris Drug Amendments (1962):** News reports about the role of an FDA medical officer in keeping the drug thalidomide off the U.S. market aroused public interest in drug regulation. Thalidomide had been associated with the birth of thousands of malformed babies in Western Europe. In October

1962, Congress passed these amendments to tighten control over drugs. Before marketing a drug, firms now had to prove not only safety, but also effectiveness for the product's intended use. In addition, firms were required to send adverse reaction reports to the FDA, and drug advertising in medical journals was required to provide complete information to doctors—the risks, as well as the benefits. The amendments also required that informed consent be obtained from the study subjects. (Note: In July 1998, thalidomide was approved by the FDA with significant restrictions. Because of thalidomide's potential to cause birth defects, FDA invoked unprecedented regulatory authority to tightly control the marketing of the product in the United States.)

- **Orphan Drug Act (1983):** "Orphans" are drugs and other products for treating rare diseases. They may offer little or no profit to the manufacturer, but may benefit people with these diseases. To foster



The "Elixir Sulfanilamide" tragedy of 1937 ensured enactment the following year of the Federal Food, Drug, and Cosmetic Act. More than 100 died from using the untested, poisonous new drug formulation, but FDA had legal authority to bring only a trivial charge of misbranding against the manufacturer. The product was labeled an "elixir," which implied it was an alcoholic solution; actually, it was a diethylene glycol solution. If the term "solution" had been used instead, no charge of breaking the law could have been made.

development, this law allows drug companies to take tax deductions for about three-quarters of the cost of their clinical studies.

- **Drug Price Competition and**

### **Patient Term Restoration Act**

**(1984):** This law expands the number of drugs suitable for an abbreviated new drug application (ANDA). ANDAs make it less costly and time-consuming for generic drugs to reach the market. Patient Term Restoration refers to the 17 years of legal protection given a firm for each drug patent. Some of that time allowance is used while the drug goes through the approval process.

- **Generic Drug Enforcement Act**

**(1992):** This law imposes debarment and other remedies for criminal convictions based on activities relating to the approval of ANDAs.

- **Prescription Drug User Fee Act**

**(1992):** In this law, manufacturers agreed to pay user fees for certain new drug applications and supplements, an annual establishment fee, and annual product fees. Using these funds, FDA hired more than 700 new staff by the end of FY 1997, which helped quicken the NDA review process.

- **FDA Modernization Act (1997):**

This act contains some of the most sweeping changes to the Food, Drug and Cosmetic Act in 35 years. Of significant importance to CDER is the reauthorization of PDUFA through FY 2002. The act contains changes in how user fees are assessed and collected. For example, fees are waived for the first application for small businesses, orphan products, and pediatric supplements. The act codifies FDA's accelerated approval regulations and requires guidance on fast-track policies and procedures. In addition, the agency must issue guidance for NDA reviewers.

## **The Review Team**

The members of the CDER review team simultaneously apply their special technical expertise to the review of an NDA:

- Chemists focus on how the drug is made and whether the manufacturing, controls, and packaging are adequate to ensure the identity, strength, quality, and purity of the product.
- Pharmacologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies.
- Physicians evaluate the results of the clinical tests—including the drug's adverse as well as therapeutic effects and whether the proposed labeling accurately reflects the effects of the drug.
- Pharmacokineticists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized, and eliminated.
- Statisticians evaluate the designs for each controlled study and the analyses and conclusions of safety and effectiveness based on the study data.
- Microbiologists with others evaluate the data on anti-infectives (antibodies, antivirals, and antifungals). These drugs differ from others in that they affect the workings of microbes instead of patients. Reviewers need to know how the drug acts on these microorganisms, which ones it affects, any resistance to the drug, and clinical laboratory methods needed to evaluate the drug's effectiveness. Microbiologists also are concerned with ensuring injectable drugs are free of organisms.

## **A Drug Review Glossary**

### **Abbreviated New Drug**

**Application, or ANDA:** A simplified submission permitted for a duplicate of an already approved drug. ANDAs are for products with the same or very closely related active ingredients, dosage form, strength, administration route, use and labeling as a product that has already been shown to be safe and effective. It must contain evidence that the duplicate drug is bioequivalent (see "Bioequivalence") to the previously approved drug.

**Accelerated Approval:** A highly specialized mechanism intended to speed approval of drugs promising significant benefit over existing therapy for serious or life-threatening illnesses. In accelerated approval, CDER approves the drug on the condition that the sponsor study the actual clinical benefit of the drug.

**Action Letter:** An official communication from FDA to an NDA sponsor that informs of a decision by the agency. An approval letter allows the commercial marketing of the product. An approvable letter lists minor issues to be resolved before approval can be given. A non-approvable letter describes important deficiencies that preclude approval unless corrected.

**Adverse Event:** Unwanted effects that occur and are detected in populations. The term is used whether there is or is not any attribution to a drug or other cause.

**Advisory Committee:** A panel of outside experts convened periodically to advise CDER on safety and efficacy issues about drugs. CDER is not bound to take committee recommendations but usually does.

**Amendment to an NDA:** A submission to change or add information to an NDA or supplement not yet approved.

**Bioavailability:** Rate and extent to which a drug is absorbed or is otherwise available to the treatment site in the body.

**Bioequivalence:** Scientific basis on which generic and name-brand drugs are compared. To be considered bioequivalent, the bioavailability of two products must not differ significantly when the two products are given in studies in the same dosage under similar conditions.

**Clinical Trials:** Human studies designed to distinguish a drug's effect from other influences—for example, a spontaneous change in disease progression or in the effect of a placebo (an inactive ingredient that looks like the test drug). Such studies conducted in the United States must be under an approved IND (see “Investigational New Drug Application”) and in accord with FDA rules on human studies and informed consent of participants.

**Compound:** A chemical synthesized or prepared from natural sources that is evaluated for its biological activities in preclinical tests.

**Dosage Form:** The delivery system for a drug product, such as tablet, capsule, IV solution, or topical cream.

**Dose:** The amount of drug administered to a patient or test subject at a single time.

**Drug Products:** The finished dosage form that contains a drug substance—generally, but not necessarily in association with other active or inactive ingredients.

**Drug Substance:** The active ingredient to diagnose, treat, cure, or prevent disease or affect the structure or function of the body, excluding other inactive substances used in the drug product.

**Effectiveness:** The desired measure of a drug's influence on a disease condition. Effectiveness must be proven by substantial evidence consisting of adequate and well-controlled investigations, including human studies by qualified experts, that prove the drug will have the effect claimed in its labeling.

**Good Laboratory Practices, or GLP:** FDA guidelines governing the conduct of nonclinical studies from which data will be used to support applications for research or marketing permits.

**Incidence Rate:** The rate at which new cases of disease, adverse reactions, or other events occur per unit of time in a given population at risk. The rate is theoretically calculated as the number of individuals who develop the disease over a period of time divided by the total person-years at risk.

**Informed Consent:** The voluntary consent given by a patient to participate in a study after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

**Investigational New Drug Application, or IND:** An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

**New Drug:** A drug first investigated or proposed for marketing after 1938—that is, a drug that was not generally recognized as safe and effective before that date.

**New Drug Application, or NDA:** An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for CDER review—including chemistry, pharmacology, medical, biopharmaceutics, statistics and, for anti-infectives, microbiology.

**New Molecular Entity, or NME:** A compound that can be patented, which has not been previously approved.

**Parallel Track Mechanism:** Policy that makes promising investigational drugs for AIDS and other HIV-related diseases more widely available under “parallel track” protocols, while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are conducted. The system established by the policy is designed to make the drugs more widely available to patients with these illnesses who have no therapeutic alternatives and cannot participate in the controlled clinical trials.

**Pharmacology:** The science that deals with the effect of drugs on living organisms.

**Phase 1:** The first trials in humans that test a compound for safety, tolerance and pharmacokinetics. The trials usually employ normal, healthy volunteers.

**Phase 2:** Pilot studies to define efficacy and safety in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Dose and dosing regimens are assigned for magnitude and duration of effect during this phase.

**Phase 3:** Expanded clinical trials intended to gather additional evidence of effectiveness for specific indications and to better understand safety and drug-related adverse effects.

**Phase 4:** Studies performed after a drug is approved for marketing. The studies are performed to determine the incidence of adverse reactions; to determine the long-term effect of a drug; to study a patient population not previously studied; and for marketing comparisons against other products and other uses.

**Postmarketing Surveillance:** FDA's ongoing safety monitoring of marketed drugs.

**Preclinical studies:** Studies that test a drug on animals and other nonhuman test systems. Since animals have a much shorter lifespan than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on its offspring.

**Priority Drugs:** A drug that appears to represent an advance over available therapy.

**Raw Data:** Researcher's records of patients such as patient charts, hospital records, x-rays and attending physician's notes. CDER may request the data's submission or may audit the data at the researcher's office.

**Risk:** The probability of an event occurring during a specified period of time. In drug approval, it is a measure of the probability of occurrence to harm human health or of the severity of harm that may occur.

**Safety:** No drug is completely safe or lacking the potential for side effects. Before a drug may be approved for marketing, the law requires the submission of test results adequate to show the drug is safe under the conditions of use in the proposed labeling.

**Safety Update Reports:** Reports that an NDA sponsor must submit to CDER about the safety information that may affect the use for which the drug will be approved, or draft labeling statements about contraindications, warnings, precautions, and adverse reactions.

**Side Effect:** Any effect other than the primary intended effect resulting from drug or nondrug treatment or intervention. Side effects may be negative, neutral, or positive for the patient.

**Stability:** The drug product's resistance to change of its physical and chemical properties.

**Supplement:** A marketing application submitted for changes in a product that already has an approved NDA. CDER must approve all important NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are not adversely affected.

**Surrogate Endpoint:** A laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions, or survives, but nevertheless is considered likely to predict therapeutic benefit.

**Treatment IND:** A mechanism that allows investigational drugs to be used in expanded access protocols: relatively unrestricted studies in which the intent is to learn more about the drugs and to provide treatment for people with immediately life-threatening or otherwise serious diseases for which there is no real alternative.

**User Fees:** Charges to drug firms for certain NDAs, drug products, and manufacturing establishments. FDA uses these fees to hire application reviewers and to accelerate reviews using computer technology.